

Amendment to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

1.- 14. (canceled)

15. (currently amended) A method for testing a compound for activity as an agonist or antagonist of a voltage-gated calcium ion channel, comprising the steps of:

(a) contacting a cell co-expressing a ~~functional~~ voltage-gated calcium ion channel and an inward rectifier potassium channel with a solution having a potassium concentration where the membrane potential of the cell is modulated without fully depolarizing the cell;

(b) simultaneous to or subsequent to step (a), contacting the cell with (i) a substance of interest and (ii) an ion or molecule capable of entering the cell through a ~~functional~~ said voltage-gated calcium ion channel;

(c) depolarizing the cell membrane of the cell;

(d) detecting the channel mediated ion flux into the cell; and

(e) comparing the ion flux thus detected from step (d) to an ion flux produced in a control experiment, wherein the control experiment comprises subjecting a separate cell to the steps (a), (b)(ii), (c) and (d), but not step (b)(i);

where a difference in ion flux detected in step (d) and the control experiment indicates that the substance of interest is an agonist or antagonist of a calcium channel.

16. (currently amended) The method of claim 15 wherein said voltage-gated calcium ion channel is the L-type calcium channel complex comprising ~~selected from the group consisting of~~ alpha 1C, alpha 2-delta and beta 2a.

17. (previously presented) The method of claim 15 wherein said inward rectifier potassium channel is the Kir 2.3 inward K⁺ rectifying channel .

18. (previously presented) A method of identifying state-dependent antagonists of a voltage-gated calcium ion channel comprising:

(a) providing a divided tissue culture plate comprising individual compartments, where at least two of the individual compartments contain living eukaryotic cells that co-express a plurality of voltage-gated calcium ion channels and inward rectifying potassium channels on their plasma membranes, the cytoplasm of the cells comprising an ion-sensitive fluorescent indicator compound;

(b) adjusting the membrane potential of the cells by altering the extracellular potassium concentration in the compartments containing said cells;

(c) adding a substance of interest to the compartments containing said cells;

(d) depolarizing said cells in at least two compartments, wherein at least one compartment is subjected to step (c), i.e. the test group, and at least one compartment is not subjected to step (c), i.e. the control group;

(e) detecting the ion flux into the cells of step (d); and

(f) comparing the ion flux into the cells of the test group with that of the cells of the control group;

where, if the value of ion flux in the test group cells is lower than that of the control group, then the substance is an antagonist of a voltage-gated calcium ion channel.

19. (currently amended) The method of claim 18 wherein said voltage-gated calcium channel is the L-type calcium channel complex comprising ~~selected from the group consisting of~~ alpha 1C, alpha 2-delta and beta 2a.

20. (previously presented) The method of claim 18 wherein said inward rectifier potassium channel is the Kir 2.3 inward K⁺ rectifying channel.

21. (previously presented) The method of claim 18 where said eukaryotic cells are HEK293 cells stably transfected to express the alpha-1C subunit of the voltage-gated calcium ion channel and the Kir 2.3 inward K⁺ rectifying channel (C1-6-37-3 cells).

22. (previously presented) The method of claim 18 wherein the substance is identified as an antagonist when the current flow into the cells of the test group is lower than the current flow into the cells of the control group.

23. (previously presented) The method of claim 18 wherein the fluorescent indicator compound is selected from the group consisting of fluo-3, fura-2, fluo-4, fluo-5, calcium green-1, Oregon green, 488 BAPTA, SNARF-1, and indo-1.

24. (previously presented) The method of claim 18 wherein the detecting step (e) employs a fluorescence or luminescence indicator device.

25. (previously presented) The method of claim 25, wherein the detecting step (e) employs a FLIPR or VIPR device.

26. (previously presented) The method of claim 18 where the detecting step (e) employs the use of FRET.

27. (previously presented) A method of identifying state-dependent antagonists of a voltage-gated calcium ion channel comprising:

(a) providing a divided tissue culture plate comprising individual compartments, where at least two of the individual compartments contain living eukaryotic cells that co-express a plurality of α_1C calcium ion channels and Kir 2.3 inward rectifying potassium channels on their plasma membranes, the cytoplasm of the cells comprising an ion-sensitive fluorescent indicator compound;

(b) adjusting the membrane potential of the cells by altering the extracellular potassium concentration in the compartments containing said cells;

(c) adding a substance of interest to the individual compartments containing said cells;

(d) depolarizing said cells in at least two compartments, wherein at least one compartment is subjected to step (c), i.e. the test group, and at least one compartment is not subjected to step (c), i.e. the control group;

(e) detecting the ion flux into the cells of step (d); and

(f) comparing the ion flux into the cells of the test group with that of the cells of the control group;

where, if the value of ion flux in the test group cells is lower than the control group cells, then the substance is an antagonist of a voltage-gated calcium ion channel.

28. (previously presented) The method of claim 27 further comprising comparing the ion flux in the test group with the ion flux obtained from a second test group, the second test group comprising cells subjected to steps (b) and (c), but whose membrane potentials have been adjusted to a value different from that of the test group;

where, if the value of the ion flux in the test group is different than the value of the ion flux in the second test group, then the substance possesses a state-dependent potency on a voltage-gated calcium ion channel.

29. (previously presented) A method of identifying antagonists possessing state-dependent potency for a voltage-gated calcium ion channel comprising:

(a) providing a divided tissue culture plate comprising individual compartments, where at least two of said individual compartments contain living eukaryotic cells that co-express a plurality of voltage-gated calcium ion channels and inward rectifying potassium channels on their plasma membranes, the cytoplasm of the cells comprising an ion-sensitive fluorescent indicator compound;

(b) adjusting the membrane potential of a first group of cells, i.e. the first test group, and a second group of cells, i.e. the second test group, by altering the extracellular potassium concentration in the individual compartments containing said cells, wherein the membrane potential of the second test group is lower than the value of the first test group;

(c) adding a substance of interest to the individual compartments containing said cells;

(d) depolarizing the cells in the at least two compartments containing said cells;

(e) detecting the ion flux into the cells of step (d); and

(f) comparing the ion flux in the cells of the first test group with that of the cells of the second test group;

where, if the value of the ion flux in the first test group is different than the value of the ion flux in the second test group, then the substance possesses state-dependent potency for said voltage-gated calcium ion channel.